PATENT SPECIFICATION (11) 1445524

1445524

(21) Application No. 4392/74 (22) Filed 30 Jan. 1974

(31) Convention Application No. 7303503 (32) Filed 1 Feb. 1973 in

(33) France (FR)

(44) Complete Specification published 11 Aug. 1976

(51) INT CL² C07D 491/04 A61K 31/535 31/54 C07D 513/04// (C07D 491/04 221/00 307/00 333/00) (C07D 513/04 221/00 307/00 333/00)

(52) Index at acceptance

C2C 1485 151X 214 220 226 22Y 246 255 256 25Y 290 29X 29Y 304 30Y 311 313 31Y 332 337 338 351 625 633 634 643 644 652 662 665 681 698 69Y 355 360 362 364 365 36Y 386 388 621 623 624 708 770 774 776 778 77X 790 79Y MM UL WC ZF

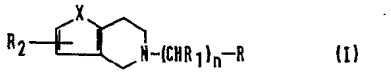
(72) Inventor ALBERT R. CASTAIGNE

(54) IMPROVEMENTS IN OR RELATING TO NEW PYRIDINE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND APPLICATIONS THEREOF

(71) We, CENTRE D'ETUDES POUR L'INDUSTRIE PHARMACEUTIQUE, a French Body Corporate of 195, Route d'Espagne, 31 Toulouse, France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new pyridine derivatives, to a process for their preparation and to their applications in human and veterinary medicine.

The new compounds of this invention have the following general formula:

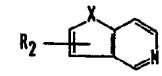


(I)

in which X represents oxygen or sulfur; R represents a phenyl radical optionally substituted with at least one halogen atom or hydroxy group, alkyl group having 1—6 carbon atoms, alkoxy group having 1—6 carbon atoms, nitro group, amino group or sulfonylamino group; R_1 represents hydrogen or a hydroxy group, an alkyl group having 1—6 carbon atoms, an alkoxy group having 1—6 carbon atoms, a nitro or an amino group; R_2 is hydrogen or halogen and n is zero or an integer from 1 to 15 and in which the symbols R_1 may have different meanings in each radical CHR_1 when n is greater than 1.

The invention includes also the acid addition salts with inorganic or organic acids and the quaternary ammonium derivatives of the derivatives of the formula (I).

The invention relates also to a process for the preparation of compounds of the formula (I) comprising condensing a compound of the formula:

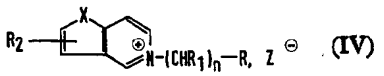


(II)

in which X and R_2 have the above meanings, with a halide of the formula

$$Z—(CHR_1)_n—R \qquad (III)$$

in which Z represents a halogen atom and R, R_1 and n have the above meanings (except in that R may also be a benzoyl group, optionally substituted as defined above for the phenyl group, in which case n is 1 to 14), to give a pyridinium salt having the formula:



(IV)

in which R, R_1, R_2, X, Z and n have the corresponding values and subsequently hydrogenating the pyridinium salt to give the derivative of the formula (I).

The resulting derivatives of the formula (I) may be isolated in free form or as salts.

The condensation reaction is preferably conducted within a medium comprising an inert solvent, such as acetonitrile, for example.

A reducing agent such as an alkali metal borohydride, e.g., sodium borohydride, will be advantageously used as hydrogenating agent. Said reduction is typically effected at room temperature.

The starting thieno[3,2-c]pyridines and furo[3,2-c]pyridines having the formula (II) are known compounds which have been described in the literature.

Purification of the products obtained by the process of this invention is preferably effected by extraction with an organic solvent such as ether after addition of a base (such as ammonia), evaporation of the solvent and workup of the residue with an acid (such as HCl) which causes precipitation as crystals which are recrystallised from ethanol, after filtration.

The salts and quaternary ammonium derivatives of the compounds of the formula (I) are prepared by methods well known by those expert in the art.

The pyridinium derivatives of the formula (IV) are also new compounds having in particular an anti-arrythmic activity and, as such, constitute a feature of the present invention.

The following non limiting examples are given to illustrate the preparation of compounds of this invention.

EXAMPLE 1

Preparation of 5 - (2 - chloro - benzyl) - 4,5,6,7 - tetrahydro - thieno[3,2-c]pyridine, as the hydrochloride (derivative 1)

A solution of thieno[3,2-c]pyridine (13.5 g; 0.1 mole) and 2 - chloro - benzyl chloride (17.7 g) in acetonitrile (150 ml) is boiled during four hours.

After evaporation of the solvent, the solid residue consists of 5 - (2 - chloro - benzyl) - thieno[3,2-c]pyridinium chloride which melts at 166°C (derivative n° 30). Said compound is taken up into a solution comprising ethanol (300 ml) and water (100 ml). Sodium borohydride ($NaBH_4$) (20 g) is added portionwise to the solution maintained at room temperature. The reaction medium is maintained under constant stirring during 12 hours and is then evaporated. The residue is taken up into water and made acidic with concentrated hydrochloric acid to destroy the excess reducing agent. The mixture is then made alkaline with ammonia and extracted with ether. The ether solution is washed with water, dried and evaporated. The oily residue is dissolved in isopropanol (50 ml) and hydrochloric acid in ethanol solution is then added thereto.

After filtration and recrystallisation from ethanol, there are obtained 5 - (2 - chloro - benzyl) - 4,5,6,7 - tetrahydro - thieno[3,2-c] pyridine hydrochloride crystals (yield: 60%) having a melting point (Koefler block) of 190°C.

EXAMPLE 2

Preparation of 5 - (4 - methoxy - benzyl) - 4,5,6,7 - tetrahydro - thieno[3,2-c]pyridine, as the hydrochloride (derivative 2)

Reacting thieno[3,2-c]pyridine (13.5 g; 0.1 mole) with 4 - methoxy - benzyl chloride (17.2 g; 0.11 mole) according to the procedure described in Example 1 gives, in a yield of 71%, hydrochloride crystals having a melting point (Koefler block) of 214—216°C.

EXAMPLE 3

Preparation of 5 - (3,4,5 - trimethoxy - benzyl) - 4,5,6,7 - tetrahydro - thieno[3,2-c] pyridine, as the hydrochloride (derivative 3)

Reacting thieno[3,2-c]pyridine (13.5 g; 0.1 mole) with 3,4,5 - trimethoxy - benzyl chloride (23.8 g; 0.11 mole), according to the procedure described in Example 1, gives hydrochloride crystals (yield: 79%) having a melting point (Koefler block) of 200—205°C.

EXAMPLE 4

Preparation of 5 - (2 - hydroxy - 2 - phenyl - ethyl) - 4,5,6,7 - tetrahydro - thieno[3,2-c] pyridine, as the hydrochloride (derivative 4)

Reacting thieno[3,2-c]pyridine (13.5 g) with phenacyl bromide (19.9 g), according to the procedure described in Example 1 (the amount of sodium borohydride is sufficient to hydrogenate both the pyridine ring and the —CO— grouping of phenacyl bromide to convert same to —CHOH—), gives hydrochloride crystals (yield: 61%) having a melting point (Koefler block) of 164—166°C.

Using analogous procedures, the following compounds were prepared:

derivative 5: 5 - parachlorobenzyl - 4,5,6,7 - tetrahydro - thieno[3,2-c]pyridine hydrochloride (m.p.=240°C);

derivative 6: 5 - parachlorobenzyl - 4,5,6,7 - tetrahydro - furo[3,2-c]pyridine hydrochloride (m.p.=210°C);

derivative 7: 5 - (3,5 - dimethoxy - benzyl) - 4,5,6,7 - tetrahydro - thieno [3,2-c]pyridine hydrochloride (m.p. 195°C);

derivative 8: 5 - (3,4,5 - trimethoxy - benzyl) - 4,5,6,7 - tetrahydro - furo [3.2-c]pyridine hydrochloride (m.p. 175°C);

derivative 9: 5 - (3 - methoxy - benzyl) - 4,5,6,7 - tetrahydro - thieno[3,2-c] pyridine hydrochloride (m.p. 200°C);

derivative 10: 5 - (3 - methyl - benzyl) - 4,5,6,7 - tetrahydro - furo[3,2-c] pyridine hydrochloride (m.p. 210—220°C);

derivative 11: 5 - (4 - methyl - benzyl) - 4,5,6,7 - tetrahydro - furo[3,2-c] pyridine hydrochloride (m.p. 220—240°C);

derivative 12: 5 - (2 - fluoro - benzyl) - 4,5,6,7 - tetrahydro - thieno[3,2-c] pyridine maleate (m.p. 197—198°C);

derivative 13: 5 - (3,4 - dichloro - benzyl) - 4,5,6,7 - tetrahydro - thieno[3,2-c] pyridine hydrochloride (m.p. 210°C);

derivative 14: 5 - (2 - phneyl - ethyl) - 4,5,6,7 - tetrahydro - thieno[3,2-c] pyridine hydrochloride (m.p. 226°C);

derivative 15: 5 - (2 - phenyl - ethyl) - 4,5,6,7 - tetrahydro - furo[3,2-c]pyridine hydrochloride (m.p. 235—240°C);
derivative 16: 5 - [(1 - methyl - 2 - hydroxy - 2 - phenyl)ethyl] - 4,5,6,7 - tetrahydro - thieno[3,2-c]pyridine hydrochloride (m.p. 230°C);
derivative 17: 5 - [(2 - parahydroxyphenyl - 2 - hydroxy)ethyl] - 4,5,6,7 - tetrahydro - furo[3,2-c]pyridine (m.p. 179°C);
derivative 18: 5 - (2 - methyl - benzyl) - 4,5,6,7 - tetrahydro - thieno[3,2-c] pyridine hydrochloride (m.p. 208—210°C);
derivative 19: 5 - (3 - methyl - benzyl) - 4,5,6,7 - tetrahydro - thieno[3,2-c] pyridine hydrochloride (m.p. 215°C);
derivative 20: 5 - (4 - methyl - benzyl) - 4,5,6,7 - tetrahydro - thieno[3,2-c] pyridine hydrochloride (m.p. 260°C);
derivative 21: 5 - (4 - fluoro - benzyl) - 4,5,6,7 - tetrahydro - thieno[3,2-c] pyridine hydrochloride, (m.p. 215°C);
derivative 22: 5 - (2,6 - dichloro - benzyl) - 4,5,6,7 - tetrahydro - thieno[3,2-c] pyridine hydrochloride (m.p. 200°C);
derivative 23: 5 - (2 - nitro - benzyl) - 4,5,6,7 - tetrahydro - thieno[3,2-c] pyridine hydrochloride (m.p. 180°C);
derivative 24: 5 - (4 - hydroxy - benzyl) - 4,5,6,7 - tetrahydro - thieno[3,2-c] pyridine hydrochloride (m.p. 240°C);
derivative 25: 5 - [(2 - parahydroxyphenyl - 2 - hydroxy)ethyl] - 4,5,6,7 - tetrahydro - thieno[3,2-c]pyridine hydrochloride (m.p. 216—218°C);
derivative 26: 5 - [(2 - paramethoxyphenyl - 2 - hydroxy) - ethyl] - 4,5,6,7 - tetrahydro - thieno[3,2-c]pyridine hydrochloride (m.p. 206—208°C);
derivative 27: 5 - [(2 - parachlorophenyl - 2 - hydroxy) - ethyl] - 4,5,6,7 - tetrahydro - thieno[3,2-c]pyridine hydrochloride (m.p. 194—196°C);
derivative 28: 5 - [(2 - hydroxy - 2 - ortho - methoxyphenyl) - ethyl] - 4,5,6,7 - tetrahydro - thieno[3,2-c]pyridine hydrochloride (m.p. 224°C);
derivative 29: 5 - [(2 - hydroxy - 2 - meta - methoxyphenyl) - ethyl] - 4,5,6,7 - tetrahydro - thieno[3,2-c]pyridine hydrochloride (m.p. 170°C).

EXAMPLE 5

Synthesis of 5 - phenacyl - thieno[3,2-c] pyridinium bromide (derivative n° 31)

A mixture of thieno[3,2-c]pyridine (13.5 g; 0.10 mole) and phenacyl bromide (19.9 g) (0.10 mole) in acetone (200 ml) is stirred during two hours at room temperature.

The resulting white precipitate is filtered, washed with acetone and dried, to give 29.7 g of crude product in a yield of 89%.

Recrystallisation of the material from water (50 ml) and drying gives 26.6 g (recrystallisation yield: 89.5%) highly hygroscopic white crystals having a melting point (Koefler block) of 206—207°C.

EXAMPLE 6

Synthesis of 5 - (o - methoxy - phenacyl) - thieno[3,2-c]pyridinium bromide (derivative n° 32)

Reaction of thieno[3,2-c]pyridine (13.5 g) with ortho - methoxy - phenacyl bromide (21.3 g) according to the procedure of Example 1 gives white crystals (27.34 g) having a melting point (Koefler block) of 258—260°C.

EXAMPLE 7

Synthesis of 2 - chloro - 5 - phenacyl - thieno [3,2-c]pyridinium bromide (derivative N° 33)

Reaction of 2 - chloro - thieno[3,2-c] pyridine (17 g) with phenacyl bromide (20 g) according to the procedure of Example 1 gives white crystals (29.60 g) having a melting point (Koefler block) of 239°C.

EXAMPLE 8

Synthesis of N - parachloro - phenacyl - thieno[3,2-c]pyridinium bromide (derivative n° 34)

Reaction of thieno[3,2-c]pyridine (13.5 g) with para - chloro - phenacyl bromide (22.5 g) according to the procedure of Example 1 gives white crystals (25.80 g) having a melting point (Koefler block) of 208—210°C.

Using analogous procedures, the following derivatives are obtained:

derivative n° 35: 5 - (3,4 - dihydroxy - phenacyl) - thieno[3,2-c]pyridinium chloride (yellowish crystals, m.p. greater than 260°C);
derivative n° 36: 5 - para - fluoro - phenacyl - thieno[3,2-c]pyridinium chloride (white crystals, m.p. 166°C);
derivative n° 37: N - (para - hydroxy - phenacyl) - thieno[3,2-c]pyridinium chloride (brown powder, m.p. 260°C);
derivative n° 38: N - (para - methoxy - phenacyl) - thieno[3,2-c]pyridinium bromide (yellowish-white crystals, m.p. greater than 260°C);
derivative n° 39: N - (meta - methoxy - phenacyl) - thieno[3,2-c]pyridinium bromide (yellow powder; m.p. 240°C).

The corresponding pyridinium derivatives of the formula (I) are prepared from derivatives 31—39 using the general procedure of Example 1 (although of course any oxo group present will be reduced to hydroxy, as in Example 4).

The results of toxicological and pharmacological tests reported below demonstrate the useful activities of the derivatives of the formula (I), particularly their anti-inflammatory

activity, their vaso-dilatator activity and their inhibitor activity on blood plate aggregation.

Thus, the invention includes also within its scope a therapeutic composition having in particular an anti-inflammatory action, a vaso-dilatator action and an inhibitor action on blood plate aggregation comprising, as active ingredient, a derivative of the formula (I) or a therapeutically acceptable acid addition salt or quaternary ammonium derivative thereof, together with a therapeutically acceptable carrier.

I. Toxicological Investigation

Said investigation demonstrated the good tolerance of the derivatives of the formula (I).

For indicative purposes, the LD_{50}/24 hrs/kg body weight, in mice, calculated according to the method of Miller and Tainter, by the intravenous route, is 60 mg for derivative n° 3, 55 mg for derivative n° 1 and 75 mg for derivative n° 8.

Orally and for all derivatives, the LD_{50}/24 hrs/kg body weight is greater than 300 mg.

The tests have shown that throughout the acute, chronic or delayed toxicity tests, the derivatives of the formula (I) have caused no local or systemic reaction and no changes in the regularly effected biological control tests.

II. Pharmacological Investigation

1. Anti-inflammatory action

Said action was investigated according to two methods.

(a) Localised carrageenin-induced edema method:

A 1% carrageenin solution (1 ml) is injected in the metatarsal flexor muscles of the right hind paw of rats at time 0.

The animals of the treated lots are additionally administered orally 100 mg/kg of the test derivative, respectively one hour prior to and then simultaneously with the phlogogenic agent, and then one hour and 2.5 hrs thereafter. The percent anti-inflammatory activity with respect to the reference lot, as a function of time, is determined by measurements effected with a Roch micrometer at times 0, one hour, two hours, three hours and five hours after carrageenin administration. The results show that with derivatives n° 8 and 5, for example, the respective percentages are 38 and 45% after one hour, 42 and 51% after two hours, 46 and 52% after three hours and 49 and 55% after five hours.

(b) Ovalbumin-induced systemic edema method

Rats are administered a simultaneous intraperitoneal injection of 1 ml ovalbumin and 0.5 ml of a $1^{o}/_{oo}$ aqueous Evans Blue solution. The animals of the treated lot are additionally administered orally 100 mg of the test derivative, one hour prior to ovalbumin administration and simultaneously with said ovalbumin administration. The intensity of the phenomenon thus induced is scored according to a scale from 1 to 5, according to the progress of the inflammatory syndrome. Thus are determined the mean intensity of the edema and the percent decrease of the edema reaction with respect to the control lot. Said percentages, for derivatives n° 8 and 5, for example, are respectively 59 and 62% after two hours and 65 and 70% after three hours.

2. Inhibitor action on blood plate aggregation

The normally cloudy blood plate rich serum of rats is made clear by addition of adenosine disphosphate which induces aggregation of the blood plates. When the same test is effected with serum taken from an animal which has been administered 100 mg/kg of a derivative having an inhibitor effect on blood plate aggregation, there is no aggregation of the blood plates and the serum remains cloudy. Thus, the inhibitor action on blood plate aggregation of the test derivatives may be evaluated by means of a simple spectrophotometric turbidimetric assay.

The tests carried out with lots of five rats (three controls and two treated animals) show that derivatives 1, 5 and 6, for example, protect the test animals against blood plate aggregation in a ratio greater than 95%.

3. Peripheral and cerebral vasodilatator action

This investigation, carried out in rabbits, demonstrated a marked vasodilatator action of the derivatives of the formula (I).

Indeed, administration (perfusion) to the test animals of a solution containing 10 mg/ml per minute, during twenty minutes, produces a substantial vasodilatation of the cerebral blood vessels. Indeed, the rheographic investigation demonstrated a marked increase of the cerebral rate of flow associated with a decrease of the peripheral vascular resistance.

It is apparent from the toxicological and pharmacological investigations reported above that the compounds of the formula (I) are endowed with a good tolerance and that they possess an anti-inflammatory activity, a vaso-dilatator activity and an inhibitor activity on blood plate aggregation.

The composition of this invention containing as active ingredient, a derivative of the formula (I), may be formulated for oral administration as tablets, coated tablets, capsules, drops or syrups. It may also be formulated as suppositories for rectal administration and as injectable solutions for parenteral administration.

Each unit dose contains advantageously from 0.025 g to 0.500 g active ingredient, the

daily dosage regimen varying within the range from 0.025 g to 1 g active ingredient.

Non limiting examples of pharmaceutical formulations of the composition of this invention are given below.

EXAMPLE 9
Tablets

Derivative n° 3	0.100 g
Talc	0.003 g
Levilite	0.010 g
Starch	0.010 g
Glucose	0.025 g

EXAMPLE 10
Coated tablets

Core	Derivative n° 1	0.080 g
	Magnesium stearate	0.010 g
	Stearic acid	0.005 g
	Corn starch	0.020 g
	Lactose	0.015 g
Coating	Rosin	0.003 g
	Turpentine	0.001 g
	Shellac	0.002 g
	Gelatin	0.005 g
	Talc	0.010 g
	White wax	0.002 g
	Titanium dioxide	0.001 g
	Erythrosine	Traces
	Officinal, white sugar, sufficient for 1 coated tablet	

EXAMPLE 11
Capsules

Derivative n° 2	0.150 g
Magnesium stearate	0.005 g
Talc	0.005 g

EXAMPLE 12
Drops

Derivative n° 5	2.5 g
Flavoured excipient, sufficient for	30 ml

EXAMPLE 13
Suppositories

Derivative n° 8	0.100 g
Semi-synthetic triglycerides, sufficient to make	1 suppository

EXAMPLE 14
Injectable solution

Derivative n° 8	0.075 g
Isotonic solution, sufficient to make	3 ml

In view of its anti-inflammatory, vasodilatator and blood plate aggregation inhibitor properties, the above composition is usefully administrable for therapeutic purposes.

In short or extended treatments, it is usefully applicable to inflammatory reactions to decrease edema, hypersecretion and exudation and to prevent the organization of the inflammatory injury. It is applicable in the treatment of post-trauma or post-surgical edema, in plastic surgery, in stomatologic surgery, in the treatment of conditions associated with inflammatory reactions (such as angina, bronchitis), in inflammatory or degenerative rheumatism and in acute abarticular conditions.

In addition, in view of its inhibitor effects on blood plate aggregation and of its vasodilator effects, it has a favourable action in the treatment of disorders of the cerebral and peripheral circulatory system and prevents thrombosis-forming complications of atheroma.

The results of toxicological and pharmacological tests reported below demonstrate the useful, particularly anti-arhythmic, activity of the derivatives of the formula (IV).

I. Toxicological investigation

Said investigation demonstrated the low toxicity of the derivatives of the formula (IV).

It concerned the acute toxicity, the subacute toxicity, the chronic toxicity, the tolerance and the teratology of said derivatives.

For indicative purposes, the LD_{50}/24 hrs/kg body weight in mice, by the intravenous route, is 19 mg for derivative n° 31, 18 mg for derivative n° 32, 38 mg for derivative n° 33, 17.5 mg for derivative n° 34, 16 mg for derivative n° 36, 25 mg for derivative n° 37, 32 mg for derivatives n° 38 and 16 mg for derivative n° 39.

The subacute and chronic toxicity tests together with the tolerance tests carried out in rats and dogs have shown that the derivatives of the formula (IV) were free from any noxious action; indeed, both the biological examinations carried out during the tests and the macroscopic and pathologic study of the animals sacrificed at the end of the experiments failed to disclose any anomaly in the treated animals.

The teratologic investigation was carried out in mice, rats and rabbits. It showed that the derivatives of the formula (IV) were free from any effect on the fecundation and the gestation of the female animals and produced no modification of the morphologigcal appearance of the young born during such experimentation.

II. Pharmacological investigation

The derivatives of the formula (IV) possess important anti-arrhythmic properties.

The tests carried out in rabbits and dogs, according to the method of Schmitt H. and H. Schmitt [Arch. Int. Pharmacodyn., 1960, 127 (1,2)], have shown that at an oral dosage of 5 mg/kg said derivatives protected com-

pletely the test animals against arrhythmia induced by barium chloride administration.

There are no regular or dispersed extrasystole bursts in the protected animals.

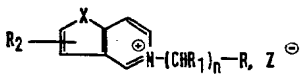
The same inhibition is also found with respect to other arrhythmia-producing agents such as calcium chloride, K-strophantine, aconitine, isoprenaline, adrenaline and ouabaine.

The anti-arrhythmic properties of the compounds of the formula (IV) were also investigated by a different method. Rhythm disorders were produced in dogs by ligation of a coronary artery.

It was shown that administration of a derivative of the formula (IV) was capable of restoring the sinus rhythm and of improving the perturbed electric activity of the heart by causing a reappearance of a rhythmic ventricular activity.

The toxicological and pharmacological investigations reported above demonstrate the good tolerance of the compounds of the formula (IV) and their outstanding anti-arrhythmic action.

Thus, the invention includes also within its scope a therapeutic composition having in particular an anti-arrhythmic activity, containing, as active ingredient, a compound of the formula



in which X, R, R_1, R_2, Z and n have the previously defined meanings, and a therapeutically acceptable carrier.

This composition containing a derivative of the formula (IV) may be formulated for oral administration as tablets, coated tablets, capsules and drops. It may also be formulated as suppositories for rectal administration and as injectable ampoules for parenteral administration.

Each unit dose contains advantageously from 0.005 to 0.100 g of derivative of the formula (IV) together with therapeutically compatible excipients, the daily dosage regimen varying within a range from 0.005 g to 0.300 g.

Non limiting examples of pharmaceutical formulations of the above composition are given below.

EXAMPLE 15
Coated tablets

Core	Derivative n° 31	0.025 g
	Talc	0.010 g
	Lactose	0.005 g
	Magnesium stearate	0.005 g
	Kaolin	0.003 g
	Starch	0.005 g
	Titanium dioxide	0.002 g
Coating	Starch	0.010 g
	Gum arabic	0.005 g
	White shellac	0.001 g
	White wax	0.002 g
	Sugar syrup sufficient to make 1 coated tablet	

EXAMPLE 16
Tablets

Derivative n° 36	0.075 g
Magnesium hydrocarbonate	0.020 g
Corn starch	0.010 g
Calcium carboxymethyl cellulose	0.005 g
Magnesium stearate	0.003 g
Stearic acid	0.003 g
Talc	0.003 g

EXAMPLE 17
Capsules

Derivative n° 33	0.100 g
Wheat starch	0.025 g
Talc	0.010 g
Lactose	0.010 g

EXAMPLE 18
Drops

Derivative n° 37	5.00 g
Flavoured excipient, sufficient for	100 ml

EXAMPLE 19
Suppositories

Derivative n° 31	0.025 g
Semi-synthetic triglycerides, sufficient to make	1 suppository

EXAMPLE 20
Injectable ampoules

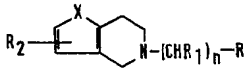
Derivative n° 31	0.010 g
Isotonic solvent, sufficient to make	3 ml

In view of their anti-arrhythmic action, the derivatives of the formula (IV) are usefully applicable therapeutically whenever it is desired to obtain an anti-arrhythmic action either on a healthy heart or on rhythm disorders subsequent to a previous infarction. They exhibit good clinical and biological tolerance, in view of the fact that no signs of blood, renal or liver toxicity could be detected by the routine examinations effected on the patients undergoing treatment.

They are applicable in cardiology in cases of ventricular tachycardia, of ventricular extrasystoles, and in disorders of the cardiac rhythm due to post-digitalization myocardial hyperexcitability. They are also anesthesiologically applicable in the preparation for heart surgery, and for general surgery in old people.

WHAT WE CLAIM IS:—

1. Pyridine derivatives having the formula:



(I)

in which X represents oxygen or sulfur; R represents a phenyl radical optionally substituted with at least one halogen atom or hydroxy group, alkyl group having 1—6 carbon atoms, alkoxy group having 1—6 carbon atoms, nitro group, amino group or sulfonylamino group; R_1 represents hydrogen or a hydroxy group, an alkyl group having 1—6 carbon atoms, an alkoxy group having 1—6 carbon atoms, a nitro group or an amino group, R_2 is hydrogen or halogen and n is zero or an integer from 1 to 15, and in which the symbols R_1 may have different meanings in each radical CHR_1 when n is greater than 1; their acid addition salts and their quaternary ammonium derivatives.

2. 5 - (2 - Chloro - benzyl) - 4,5,6,7 - tetrahydro - thieno[3,2-c]pyridine and its acid addition salts.

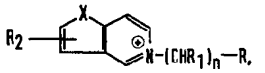
3. 5 - (4 - Methoxy - benzyl) - 4,5,6,7 - tetrahydro - thieno[3,2-c]pyridine and its acid addition salts.

4. 5 - 3,4,5 - Trimethoxy - benzyl) - 4,5,6,7 - tetrahydro - thieno[3,2-c]pyridine and its acid addition salts.

5. 5 - para - Chlorobenzyl - 4,5,6,7 - tetrahydro - thieno[3,2-c]pyridine and its acid addition salts.

6. 5 - (2 - Fluoro - benzyl) - 4,5,6,7 - tetrahydro - thieno[3,2-c]pyridine and its acid addition salts.

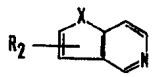
7. Pyridinium derivatives having the formula:



(IV)

in which X represents oxygen or sulfur; R represents a phenyl or benzoyl radical optionally substituted with at least one halogen atom or hydroxy group, alkyl group having 1—6 carbon atoms, alkoxy group having 1—6 carbon atoms, nitro group, amino group or sulfonylamino group; R_1 represents hydrogen or a hydroxy group, an alkyl group having 1—6 carbon atoms, an alkoxy group having 1—6 carbon atoms, a nitro or amino group; R_2 represents hydrogen or halogen, n is zero or an integer from 1 to 15 (except in that n is 1 to 14 when R is benzoyl), and in which the symbols R_1 may have different meanings in ecah radical CHR_1 when n is greater than 1, and Z represents halogen.

8. Process for the preparation of derivatives as claimed in claim 1, comprising condensing a compound of the formula:

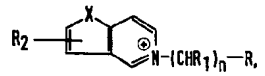


(II)

in which X and R_2 have the meanings defined in claim 1, with a halide of the formula:

$$Z—(CHR_1)_n—R \qquad (III)$$

in which Z represents a halogen atom and R, R_1 and n are as defined in claim 7, to give a pyridinium salt having the formula:



(IV)

in which R, R_1, R_2, X, Z and n are as defined in claim 7 and then hydrogenating the resulting pyridinium salt to give the derivative of the formula (I).

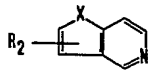
9. Process as claimed in claim 8, wherein the condensation reaction is effected in an inert solvent.

10. Process as claimed in claim 9, wherein said inert solvent is acetonitrile.

11. Process as claimed in claim 8, wherein the hydrogenation is effected with a reducing agent.

12. Process as claimed in claim 11, wherein said reducing agent is an alkali metal borohydride.

13. Process for the preparation of derivatives as claimed in claim 7, comprising condensing a compound of the formula:



(II)

in which X and R_2 have the meanings defined in claim 7, with a halide of the formula

$$Z—(CHR_1)_n—R$$

in which Z, R_1, R and n are as defined in claim 7.

14. Process as claimed in claim 13, wherein the condensation reaction is effected in an inert solvent.

15. Process as claimed in claim 14, wherein said inert solvent is acetonitrile.

16. Therapeutic composition comprising, as active ingredient, a derivative of the formula (I) as claimed in claim 1 or a pharmaceutically acceptable acid addition salt or quaternary ammonium derivative thereof, together with a therapeutically acceptable carrier.

17. Therapeutic composition as claimed in claim 16, in unit dosage form, each unit dose containing from 0.025 g to 0.500 g active ingredient.

18. Therapeutic composition comprising, as active ingredient, a pyridinium derivative as claimed in claim 7, and a therapeutically acceptable carrier.

19. Therapeutic composition as claimed in claim 18, in unit dosage form, each unit dose containing from 0.005 g to 0.100 g active ingredient.

20. Pyridine derivatives as claimed in claim 1, substantially as described with reference to Examples 1—4.

21. Pyridinium derivatives as claimed in claim 7, substantially as described with reference to Examples 5—8.

22. Process of preparation of pyridine derivatives as claimed in claim 8, substantially as described.

23. Process of preparation of pyridinium derivatives as claimed in claim 13, substantially as described.

24. Therapeutic composition as claimed in claim 16, substantially as described with reference to Examples 9—14.

25. Therapeutic composition as claimed in claim 18, substantially as described with reference to Examples 15—20.

For the Applicants,
FRANK B. DEHN & CO.,
Chartered Patent Agents,
Imperial House,
15—19, Kingsway,
London, W.C.2.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1976.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.